DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

M-2677N

19900 MacArthur Blvd., Ste 300
Irvine, California 92612-2445
Telephone (949) 798-7600

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

November 24, 1998 W/L 13-9

Richard Wallin, President and CEO
North American Science Associates (NAmSA)
2261 Tracy Road
Northwood, Ohio 43619-1397

Dear Mr. Wallin:

During an inspection of your contract testing laboratory, located in Irvine, California, which was conducted September 21-25, 1998, our investigators documented serious deviations from the Current Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations (CFR) Parts 210 and 211). These deviations cause the drug products tested by your facility to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act).

Failure to maintain facilities in a state of good repair [21 CFR 211.58] in that our investigators observed rust on the HEPA filter supports and class [redacted] laminar flow hood legs and they observed flaking paint from light fixtures in sterility suites [redacted] which are class [redacted] rooms (FDA 483 observation IV.1a).

Failure to maintain adequate controls over computers and related systems to assure that changes in the master production and control records or other records are instituted only by authorized personnel [21 CFR 211.68(b)]. For example: (1) there is no current listing of individuals who have access to the Customer Service Unit's [redacted] database program or to what level of access each individual has; (2) there is no procedure in place to grant, modify or remove access privileges to this software (FDA 483 observation 1 d&e).

Failure to maintain complete data from all tests necessary to assure compliance with established specifications and standards [21 CFR 211.94]. For example:

(a) The Customer Service Unit's (CSU) [redacted] database program which generates the sample test worksheets that are identified by sequential sample numbers, allows for the multiple printing of these worksheets. Copies will have the same sample number as the

original without any indication which version is the original and which is a subsequent copy. Further, there is no audit trail within the computer that identifies how many worksheets have been generated for a given sample number (FDA 483 observation I.1f).

(b) A number of worksheets and logs used to record raw data were available in the appropriate laboratories without any mechanism controlling their use (FDA 483 observation V.2).

(c) The procedure entitled "Approval of Raw Data" (L27-01) issued 9/16/98, allows for managers to approve their own work. Therefore, work they perform and approve does not require the initials and signature of a second person showing that the work has been reviewed for accuracy, completeness and compliance with standards (FDA 483 observations VI.2 & VIII.2).

(d) The report entitled "NAMSA Revalidation of Steam Sterilization-[redacted] Autoclaves [redacted] indicates that the purpose of the revalidation was to determine the temperature distribution for the empty chamber and representative media load configurations, determine the relationship between the autoclave controller time temperature conditions and the time temperature conditions for the "cold spot" in representative media load configurations and to define the biological lethality of the sterilization cycle for representative media load configurations. No raw data was presented to FDA investigators indicating that cold spot mapping was ever performed (FDA 483 observation III.4).

Failure to establish, maintain or follow adequate laboratory controls and to always record and/or justify deviations from these testing procedures and control mechanisms [21 CFR 211.160]. For example:

(a) The validation of the Biotech Suite (Sterility Suite 2) was inadequate in that there were no pre-defined criteria describing what the requirements of the suite, other than that of environmental monitoring, were to be, nor were there any pre-defined criteria describing what the requirements for the equipment of this suite were to be. Additionally, there was no discussion, conclusions or follow-up to environmental monitoring excursions that occurred during the validation study (FDA 483 observations III. 1&2).

(b) There was no installation, operation or performance qualification performed for the [redacted] incubators [redacted] (FDA 483 observation III.5).

(c) The procedure entitled "[redacted]" (M-GP95-05) is not always followed. Re-tests are being performed without the appropriate number of replicates or test articles being included in the re-test (FDA 483 observation VIII.1).

(d) The procedure entitled "Failure Investigations" (L18-01) does not define a procedure for conducting such investigations (FDA 483 observation VIII.3a).

(e) The procedure entitled "Equipment Qualification" (L22-02) does not clearly explain the yearly requirement for the re-qualification of instruments. In one sentence of Section III.Q this procedure states that "all equipment not mentioned in Section IV.B. must be re-qualified at least annually." The following sentence states "the re-qualification performed is at the discretion of the department....." This could be interpreted to mean that a department head could decide not to re-qualify an instrument after major changes or on a yearly basis (FDA 483 observation II.1a & III.3).

(f) There are no formal written procedures defining training, qualification, disqualification and re-qualification of sterility suite operators when they exceed the microbial limits defined in the procedure entitled "Sterility Test Facility-Environmental Testing" (M-ST03-06). For example, your current practice is to monitor operators who exceed the microbial limits for three consecutive days following the excursion instead of the routine monthly monitoring. In at least two cases in May 1998, individuals who were being monitored for three consecutive days as a result of excursions exceeded the microbial limits within the three-day monitoring period. The corrective action following this second excursion was to monitor them for an additional three days (FDA-483 observation IV.1c).

(g) There are no formal written procedures for gowning prior to entering the sterility suites (FDA-483 observation IV.1d).

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. A list of observations (Form FDA-483) was issued and discussed with you at the conclusion of the inspection. It is your responsibility to assure adherence with each requirement of the current Good Manufacturing Practice regulations and other applicable regulations.

In addition to the above-listed violations, we have the following comments:

We realize that your firm is a contract testing laboratory and as such does not have ultimate responsibility for the drug products tested. However, 21 CFR 210.3(b)(12) defines testing as part of the drug product manufacturing, processing, packaging and holding process. Therefore, your firm is subject to the CGMP requirements which pertain to the testing processes performed.

We are concerned that your computer system allows for the generation of multiple copies of sample test worksheets without identifying which is the original copy and which are not. Additionally, your computer system does not provide an audit trail that can identify the number of worksheets with a given sample number that have been generated. We are also concerned with the uncontrolled worksheets and logs used for recording raw data which are available in the appropriate laboratories

(FDA-483 observation V.2). This failure to control documents on which data is recorded could allow original data to be lost or manipulated without any means of detection.

In regards to failure investigations and re-testing (Form FDA 483 observation VIII) the procedure for failure investigations should describe the general procedure to follow during a failure investigation. If re-testing is determined to be appropriate by the investigational findings, this procedure should specify the appropriate number of re-tests and what constitutes ultimate failure of the test.

During the inspection FDA investigators asked who was responsible for the annual re-qualification of the DI/RO water system and who was responsible for the examination and maintenance of the sterility suites. Your firm could not give a definitive answer as to who was responsible for the annual re-qualification of this water system nor did your employees appear to have clear knowledge of where the responsibility lay for examination and maintenance of the sterility suites. Our investigators also determined that a number of your employees do not appear to have a clear understanding as to how their job functions relate to current GMPs. There should be a clear understanding among your managers and Quality Assurance personnel as to where the responsibility for facilities, systems, and instrumentation examination and maintenance lies. Additionally, all employees should be trained in and aware of the current GMPs in general and should have specific knowledge of those associated with the performance of their jobs.

You should take prompt measures to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. This may include seizure and/or injunction.

Please notify this office in writing within 15 working days of receipt of this letter regarding the specific steps you have taken to correct the above violations, including an explanation of each step being taken to prevent recurrence of similar violations. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Your response should be sent to:

Thomas L. Sawyer, Compliance Director
U.S. Food and Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612-2445

We acknowledge your response, dated October 13, 1998, to the Form FDA-483 issued to you at the close of the inspection. This response indicates that you have already made many of the required corrections. Please confirm and document the corrections made in your response to this letter. We believe a meeting with this office would be an appropriate forum to discuss your corrective actions.

You may schedule such a meeting at a mutually convenient time by speaking with Ms. JoAnn Maney, Secretary to the District Director, at (949) 798-7774.

Sincerely,

Elaine C. Messa
District Director

cc: Dr. Darwin L. Cheney, Ph.D.
General Manager
North American Scientific Associates
9 Morgan
Irvine, CA 92618

California DHS/Food and Drug Branch
Attn: Stuart E. Richardson, Jr.
601 North 7th Street, MS-357
Sacramento, CA 94234-7320